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Appendix 1

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Appendix 2

The Cost of Prostate Cancer Chemoprevention: A Decision Analysis Model

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Abstract

Background: **The Prostate Cancer Prevention Trial found reduced prostate cancer prevalence for men treated with finasteride. The public health cost of wide-scale chemoprevention is unclear. We developed a model to help clarify the cost effectiveness of public use of prostate cancer–preventive agents.**
Methods: **A Markov decision analysis model was designed to determine the lifetime prostate health-related costs, beginning at the age of 50 years, for men treated with finasteride compared with placebo. Model assumptions were based on data from the Prostate Cancer Prevention Trial, a literature review of survival and progression rates for patients treated with radical prostatectomy, and costs associated with prostate cancer disease states.**
Results: **Chemoprevention with finasteride resulted in a gain of 13.7 life years per 1,000 men at a cost of $704,000 per life year saved (LYS). However, if finasteride is assumed to not increase the incidence of high-grade tumors, it renders a gain of 21.4 life years per 1,000 men at a cost of $434,000 per LYS; finasteride must cost $15 monthly to reach $100,000 per LYS. When applied to a population at higher risk (lifetime prevalence of ≥30%) for developing prostate cancer, the cost of finasteride must be reduced from its current cost ($62/mo) to <$15 per month for the cost effectiveness to fall below $50,000 per LYS.**
Conclusions: **Given the natural history of treated prostate cancer, implementation of chemoprevention would require an inexpensive medication with substantial cancer risk reduction to be cost effective. Targeting populations at higher risk for developing prostate cancer, however, allows for considerable flexibility in the medication cost to make prostate cancer chemoprevention a more attainable goal.** (Cancer Epidemiol Biomarkers Prev 2006;15(8):1485–9)

Introduction

The NIH estimated that the overall economic cost of cancer in the United States was $189.8 billion in 2004, with $69.4 billion attributed to direct medical costs, $16.9 billion to indirect morbidity costs, and $103.5 billion to indirect mortality costs (1). Prostate cancer is the most common nonskin malignancy and the second leading cause of cancer death among men in the United States (2) An estimated 232,090 new cases of and 30,350 deaths from prostate cancer occurred in the United States in 2005 (1). Therefore, effective prostate cancer prevention could substantially reduce overall cancer-related costs in the United States.

The Prostate Cancer Prevention Trial (PCPT) examined the ability of finasteride to prevent prostate cancer in 18,882 men who were 55 years or older (3). Finasteride inhibits 5α-reductase from metabolizing testosterone into the more potently carcinogenic androgen dihydrotestosterone and thus lowers the level of dihydrotestosterone in the prostate. PCPT participants were randomized to finasteride or a placebo and then treated and followed for 7 years. The 7-year prevalence of prostate cancer was reduced by 24.8% in the finasteride versus in the placebo group. However, there also was an increase in high-grade prostate tumors (Gleason score of ≥7) in the finasteride compared with the placebo group (37% versus 22.2%). This high-grade finding of the PCPT has complicated the assessment of competing benefits, risks, and costs and thus prevented the community-wide acceptance of finasteride for prostate cancer prevention. Indeed, no drug has been approved by the U.S. Food and Drug Administration for prostate cancer prevention to date.

We designed the current study to develop a model that can assess the financial effect on society of the public health use of a prostate cancer–preventive agent, such as finasteride, by millions of men at risk.

Materials and Methods

Markov Decision Analysis. A Markov decision analysis model was created to compare the lifetime cost associated with treating men at risk for prostate cancer with finasteride versus without finasteride. The model was designed to compare the financial effect of this cost on the public. Similar to the PCPT entry criteria, the base case was assumed to have a prostate-specific antigen (PSA) of ≤3.0 mg/mL, a normal digital rectal exam, and an American Urological Association symptom score of <20 (3). The base case is a 50-year-old man who receives daily finasteride treatment for a total of 20 years or until prostate cancer is diagnosed. As shown in Fig. 1, we assumed a simple model of disease progression that occurred in a fixed sequence of health states: (*a*) cancer free, (*b*) prostate cancer (Gleason grades 8-10, 7, 6, or 2-5), (*c*) biochemical recurrence of prostate cancer, (*d*) metastatic disease, and (*e*) death. At the conclusion of each 12-month cycle, the patient could remain in the same health state, experience progression of their disease, or die of unrelated causes. Following the diagnosis of cancer, the patient undergoes immediate radical retropubic prostatectomy and pelvic lymph node dissection without adjuvant or neoadjuvant therapy. Biochemical recurrence, when present, was managed initially with watchful waiting. No patient received early hormone ablative therapy. If the patient entered the metastatic disease health state, it was assumed that he would be treated with androgen ablation therapy using leuprolide acetate. No additional costs were added for potential use of chemotherapy because chemotherapy use is inconsistent in patients with androgen-independent prostate

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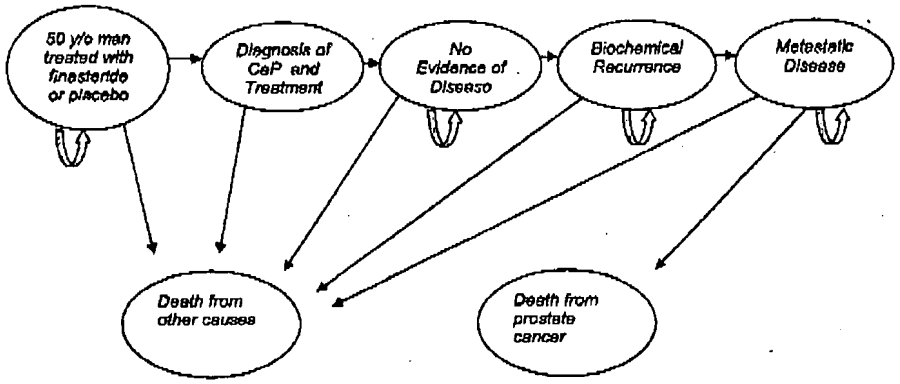

Figure 1. Markov cycle. *Circles*, various Markov states in the model. *Arrows*, transitions between disease states. Transition probabilities are shown in Table 1. *CaP*, prostate cancer.

cancer. However, an additional analysis was conducted after applying cost for salvage therapy and chemotherapy for a large number of patients diagnosed with prostate cancer. We assumed a quarter of men with prostate cancer diagnosis received salvage therapy following PSA recurrence at a cost of $15,000 and one half of men with metastatic disease received chemotherapy at a cost of $50,000. Markov modeling was designed with TreeAge Pro Healthcare (4). The lifetime cost for chemoprevention is defined as the lifetime cost of preventive medication plus the lifetime cost of prostate cancer care considering the reduced risk of developing any prostate cancer and the increased risk of developing high-grade prostate cancer on finasteride. The lifetime cost of the placebo arm is just the lifetime cost of prostate cancer treatment considering the increased risk of developing any prostate cancer and reduced risk of developing high-grade prostate cancer versus finasteride. The cost per life year saved (LYS) is the difference between the lifetime costs for the chemoprevention group and placebo group divided by the gain of life years.

Assumptions

Prostate Cancer Incidence. The prostate cancer incidence for men was based on for-cause biopsy detection rates (and excluded cancer detected in end-of-study biopsies, which were not for cause) in the placebo arm of the PCPT (3). To estimate the age-specific incidence rates for men not represented in the PCPT (age <55 years) and to determine lifetime prostate cancer incidence rates, a smooth isotonic regression curve was applied to the age-specific detection rates observed in the PCPT. Incidence rates among finasteride-treated men were derived from the placebo arm detection rates after applying a yearly relative risk reduction afforded by finasteride. Based on these factors, the estimated average lifetime probability of developing prostate cancer is 12.5% with finasteride versus 16% without finasteride. In the PCPT, men treated with finasteride were found to have an increased distribution of higher grade tumors compared with men in the placebo arm. However, there is some evidence that this distribution may be a grading bias (5-7). Therefore, we did an analysis with and without a difference in Gleason score distribution.

Outcomes Following Treatment of Prostate Cancer. The long-term progression and survival rates for patients treated with radical prostatectomy are based on literature about the natural history of treated prostate cancer (Table 1; refs. 8, 9). To approximate the outcomes of men from the PCPT, we used publications characterizing outcomes among patients with low-stage disease (T1c and T2a-b) in the PSA era when available.

Costs. Cost data are shown in Table 2 (10-14). All data were collected from cost, not charge, data. All costs were updated to 2005 U.S. dollars with the Gross Domestic Product Deflator Inflation Calculator (15). An annual discount rate of 3% was applied to future costs and future years of life (16, 17). Discounting is necessary when the experience of the patient in the near term is valued more than future costs and health outcomes (18). Medication costs were based on average manufacturer's wholesale drug price. The cost of finasteride was based on current costs at a nationwide pharmacy (ref. 19; $62/mo) and this cost accumulated until the patient was diagnosed with prostate cancer, died from other causes, or reached 70 years of age.

Cost of radical retropubic prostatectomy included the costs of hospitalization and the cost of immediate and late complications (20). Prostate cancer–related costs depend on the patient's disease status. Following retropubic prostatectomy, costs include follow-up physician visits and PSA laboratory tests. Yearly costs associated with PSA recurrence and metastases are shown in Table 2.

Effect of Finasteride on Benign Prostatic Hyperplasia. The risk reduction afforded by finasteride for preventing benign prostatic hyperplasia was based on data from the Medical Therapy of Prostatic Symptoms Trial (21). Average treatment cost for men with benign prostatic hyperplasia was based on treatment costs, including medical and surgical therapy.

Sensitivity Analysis. Sensitivity analysis was done to investigate the effect of adjusting several of the base case assumptions. Prostate cancer incidence rates found in the PCPT were used for the model to reflect a scenario of chemoprevention for men without prostate cancer at the onset

Table 1. Transition probabilities for different health states

Gleason score	No evidence of disease to biochemical recurrence, y (8)			Biochemical recurrence to metastatic disease, y (9)		Metastatic disease to prostate cancer death, y (9)	
	5	10	15	5	10	5	10
8-10	0.25	0.43	0.50	0.625	0.8125	0.50	0.875
7	0.21	0.35	0.42	0.25	0.5	0.50	0.875
6	0.15	0.25	0.31	0.25	0.5	0.50	0.875
2-5	0.12	0.20	0.23	0.25	0.5	0.50	0.875

Table 2. Assumptions on model variables, including costs of medication, disease status, treatment procedures, visits, and tests with additional assumptions on the prevalence and effectiveness of finasteride on benign prostate hypertrophy

Variable	Base case	Range in sensitivity analysis
Medications (annual costs, U.S. dollars)		
Finasteride (19)	749	713-959
Leuprolide acetate (11)	5,709	2,317-8,111
α Blocker (19)	432	288-840
Disease states (annual costs, U.S. dollars)		
Biochemical recurrence (11)	371	231-927
Metastasis (11)	463	231-927
Other (one-time cost, U.S. dollars)		
Cost of terminal care for prostate cancer (11-13)	40,744	6,714-47,601
Radical retropubic prostatectomy (20)	18,000	15,675-21,020
Complications from retropubic prostatectomy (20)	2,445	1,500-4,000
Physician visit*	60	50-100
PSA laboratory test*	7	6-60
Transurethral resection of prostate*	4,597	
Prevalence of benign prostatic hyperplasia (14)		
Age <65 y	0.15	0.10-20
Age ≥65 y	0.22	0.14-30
Relative effect of finasteride on prevalence of benign prostatic hyperplasia, % (3)	60	50-100
Discount Rate, % (16, 17)	3	1-5

*Local cost estimates.

of intervention. We did sensitivity analyses following adjustment of the cost and risk reduction provided by finasteride. In addition, chemoprevention for high-risk populations, such as men with a family history of prostate and/or men with high-grade prostatic intraepithelial neoplasia, may be more cost effective because of the increase prevalence of the disease. We examined the effects of adjusting the prevalence of prostate cancer in the population.

Results

Reduced Overall, Increased High-Grade Prostate Cancer with Finasteride. Our first analysis assumed the grade distribution of the PCPT-reduced overall prostate cancer and increased high-grade prostate cancer in the finasteride versus the placebo arm (3). Under this assumption, finasteride chemoprevention resulted in a gain of 13.7 life years per 1,000 men. At an increased lifetime cost of $9,631 per person, this renders a discounted incremental cost effectiveness ratio of $703,847 per LYS for finasteride versus no treatment.

Reduced Overall, No Increased High-Grade Prostate Cancer with Finasteride. Based on evidence that the higher distribution of Gleason score of ≥7 in the finasteride versus the placebo arm of the PCPT may have been more apparent than real, our second analysis assumed that finasteride reduces overall prostate cancer and does not increase the incidence of high-grade disease. Under this assumption, finasteride chemoprevention resulted in a gain of 21.4 life years per 1,000 men. At an increased lifetime cost of $9,607 per person, this renders a discounted incremental cost effectiveness ratio of $434,113 per LYS for finasteride versus no treatment.

Sensitivity Analysis. A two-way sensitivity analysis relaxing the assumptions about the disease prevalence and the relative risk reduction in the incidence of prostate cancer is shown in Table 3. Assuming a 25% relative risk reduction afforded by treatment, if the cost of finasteride was reduced from its current cost of $62 per month to $15 per month, the cost per LYS would fall to $52,908 for a population at high risk (prevalence of ≥30% for men age 50 years and older) of developing prostate cancer. On the other hand, at a cost of $62 per month, a relative risk reduction of 50% targeted at a population with a prostate cancer prevalence of ≥35% after the age of 50 years would be required to obtain a cost of $100,000 per LYS. Graphic representations of two-way sensitivity analyses are shown in Figs. 2 and 3. Figure 2 shows that disease prevalence and the prostate cancer risk reduction significantly affect the cost effectiveness of finasteride. At a cost of $62 per month, the cost per LYS is >$100,000 unless the prevalence is >40% and the risk reduction is >50%. In Fig. 3, cost effectiveness is based on varying drug costs and disease prevalences. At low drug costs, chemoprevention results in <$100,000 per LYS even at low disease prevalence. An additional analysis was done to bias toward an increased cost of prostate cancer treatment. We assumed a quarter of men with prostate cancer diagnosis received salvage therapy following PSA recurrence and one half of men with metastatic disease received chemotherapy. This resulted in a decrease in the cost effectiveness ratio by 3.9%.

Discussion

Finasteride produced a 24.8% reduction in prostate cancer prevalence over a 7-year period in the PCPT. The PCPT, however, also found an increased risk of high-grade disease with finasteride, which has prevented the widespread use of this agent for preventing prostate cancer. Competing benefits, risks, and costs have emerged as the major issue governing preventive agent use, and we conducted the present analysis to explore the potential effect of finasteride or any other prostate cancer prevention agent on cancer costs in the United States.

Our analysis shows that finasteride at its current cost ($62/mo) would result in a significant economic burden to society if taken by all men starting at the age of 50 years. Based on 2004 census figures, the United States has >28 million men over the age of 50 years (http://www.census.gov), and introducing a medication costing $62 per month would add billions of dollars to public health costs. The estimated "reasonable" costs per LYS fall in a wide range. In a review of cost effectiveness analyses, Earle et al. (22) noted that most studies did not specify a standard reasonable cost per LYS and that the minority of studies specifying a cost pegged it at no >$100,000 per LYS, far below the modeled finasteride costs of $703,847 per LYS (assuming increased high-grade prostate cancer with finasteride) or $434,113 per LYS (assuming no increased high-grade disease with finasteride). In analyzing the cost effectiveness of tamoxifen for high-risk women based

Table 3. Three-way sensitivity analysis assuming similar grade distribution between finasteride and placebo arms

Relative risk reduction (%)	Cost of finasteride (U.S. $/mo)	Lifetime prevalence (men diagnosed after the age of 50 years)			
		12.5% ($)	30.0% ($)	40.0% ($)	50.0% ($)
25	15	92,413	52,908	39,941	29,883
	30	211,183	117,224	86,141	61,630
	62	467,857	256,218	185,982	130,238
50	15	37,411	19,233	13,299	8,743
	30	91,753	48,435	34,133	22,901
	62	209,191	111,544	79,159	53,498
80	15	20,856	9,024	5,152	2,166
	30	56,864	27,681	18,361	11,019
	62	131,521	68,001	46,907	30,151

NOTE: Results are cost per LYS.

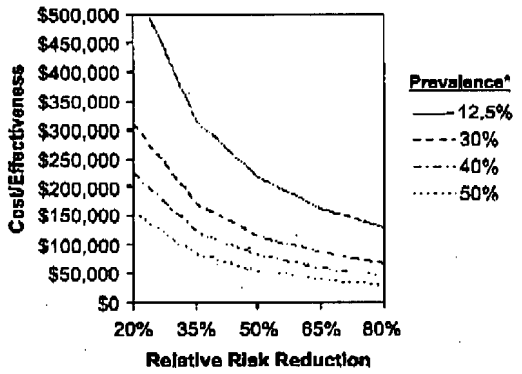

Figure 2. Two-way sensitivity analysis. Effect of relaxing assumptions about relative risk reduction and prevalence assuming finasteride cost of $62 per month. *Asterisk*, prevalence of prostate cancer ≥50 years of age.

on the Breast Cancer Prevention Trial, Hershman et al. (23) identified subgroups, in which the cost per LYS was <$50,000. The costs of finasteride and other chemoprevention agents would drop below $50,000 per LYS if used in higher risk populations and/or at lower costs as shown in Table 3. Our analysis was based on a societal perspective, and considerations for an individual at risk for prostate cancer may be quite different. Many people, especially those at a higher risk, may be willing and able to pay out-of-pocket for a chemopreventive agent with a showed prostate cancer risk reduction. A national survey documenting the prevalence and costs of alternative medicine use in the United States found that an ~15 million adults or 18.4% of all prescription users took prescription medications concurrently with herbal remedies and/or high-dose vitamins in 1997 (24). Estimated expenditures for alternative medicine professional services were conservatively estimated at $21.2 billion in 1997, with at least $12.2 billion paid out-of-pocket. Because most alternative medications have not been tested rigorously in randomized, controlled trials, it is not unreasonable to assume that rigorously evaluated medications shown to reduce cancer will be welcomed by people at risk (25). Although a medication, such as finasteride, may not be accepted due to concerns over high-grade disease, future medications may appeal to individual patients even if not cost effective from a public health standpoint.

The proportions of high-grade (Gleason score of ≥7) tumors in the PCPT were 37% in the finasteride arm and 22.2% in the placebo arm. Although certain data suggest that this finasteride-associated increase in high-grade tumors may be due to a grading bias and not to truly advanced disease, this issue is unsettled. The distribution of Gleason scores was important, however, in the survival advantage and overall cost benefit of finasteride treatment in our model. Our analysis indicates that with the Gleason score distributions found in the PCPT, finasteride could be expected to offer a survival benefit of 0.28 month per individual (versus placebo). Assuming that finasteride does not truly increase high-grade tumors, however, we found that the survival advantage would be 1.2 months per individual. This survival advantage translates into a substantial benefit if it is averaged across the population targeted for chemoprevention. For example, tamoxifen was found to reduce the risk of breast cancer by 50% in a high-risk population (26) and approved by the Food and Drug Administration for reducing the risk of primary invasive breast cancer among women at high risk (27). Survival outcome modeling of Breast Cancer Prevention Trial results found that tamoxifen could increase survival by 2.3, 1.4, and 0.9 months for individuals initiating tamoxifen at ages 35, 50, and 60 years, respectively (23).

In a previous examination of the implications of the PCPT (28), we used previously published data based on long-term outcomes for men with prostate cancer to determine the survival benefit conferred by chemoprevention with finasteride over a 15-year period. As in this analysis, we found a small but significant benefit from treatment with finasteride with population-wide gains in survival of <2 months per individual assuming no increase in high-grade cancers from finasteride. The use of Markov modeling, however, allows for a more accurate estimate of the net gains in chemoprevention. Markov modeling allows for incorporating distinct transition rates for various stages of disease based on data from patients with staging and grading characteristics similar to those in the PCPT. In addition, the model can account for lifetime benefits, including those gained or lost near the end of life. Furthermore, the present model included the time from initiating finasteride to the diagnosis of prostate cancer (based on age-specific incidence rates of the PCPT), which was not included in our previously published analysis.

The results of our study are similar to those recently reported by Zeliadt et al. (29), who also found that finasteride was not cost effective for men age 55 years or older at a cost of $233,000 per LYS assuming that finasteride prevents 25% of both high- and low-grade cancers. In the Zeliadt analysis, the prostate cancer incidence rates were based on Surveillance, Epidemiology, and End Results data. In contrast, we used incidence rates found in the PCPT to appropriately estimate rates that might be found in a population more heavily screened than the Surveillance, Epidemiology, and End Results population. Despite using different incidence rates, both models indicate that only a small proportion of the overall population develops prostate cancer. Therefore, a substantial portion of the cost is generated by giving finasteride to men who would never develop prostate cancer without finasteride. Even when applying cost for salvage therapy and chemotherapy to a large percentage of patients diagnosed with prostate cancer in our model, the cost effectiveness from finasteride changed minimally.

The benefit of a preventive intervention depends in part on the baseline risk of the population receiving it. To examine the effects of applying a chemoprevention strategy within a selected population at high risk, we did a sensitivity analysis by adjusting disease prevalence. Applying chemoprevention to a high-risk group, such as men with high-grade prostatic intraepithelial neoplasia or men with a family history of prostate cancer, would improve the cost effectiveness ratio. Therefore, this model can be used in determining appropriate target

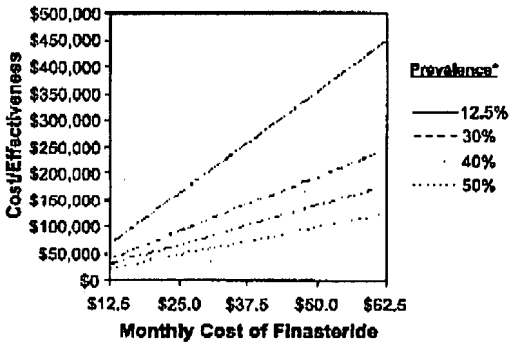

Figure 3. Two-way sensitivity analysis. Effect of relaxing assumptions about monthly cost of finasteride and prevalence assuming risk reduction 25%. *Asterisk*, prevalence of prostate cancer ≥50 years of age.

populations for chemoprevention strategies. This sensitivity analysis, however, assumes that finasteride would produce the same relative risk reduction in lower- or higher-risk populations, which is speculative. As our ability to identify high-risk populations improves and as new chemopreventive agents are discovered, it is quite possible that cost-effective agents will become available. Certainly, when the patent on finasteride ends, the cost of the drug will decrease and the cost effectiveness ratio will significantly improve, possibly making finasteride prevention in certain high-risk populations economically beneficial.

Our analysis has certain limitations. Alternative treatment modalities for the primary management of prostate cancer may vary significantly in cost. Timing and method of hormone ablative therapy can considerably affect the financial burden of the disease. In addition, other costs important from a societal perspective, such as loss of productivity or travel, were not considered. Some inaccuracy of cost and transition rates, however, is unavoidable given the variability of different practice patterns, local costs, and differences in prostate cancer outcome found in published series. For the most part, we chose the highest estimates of the cost available in terms of treatment or living with the disease to bias toward favoring treatment with finasteride. In addition, the duration of the effect from finasteride is unknown because the PCPT only evaluated patients for 7 years. We modeled the use and risk reduction of finasteride over a 20-year period (beginning in men ages 50 years old) because age 70 years is typically the cutoff used for prostate cancer screening.

In conclusion, finasteride, at its current cost, would not be cost-effective prostate cancer prevention for a population of lower-risk men ages 50 years or older. Targeting higher-risk populations, however, would increase the cost at which finasteride would become cost-effective prevention. A major current direction of prostate cancer prevention study is the development of models based on molecular and other factors that can identify high risks of prostate cancer, particularly aggressive prostate cancer (10). This work promises to make cost-effective prostate cancer chemoprevention an attainable goal.

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Appendix 3

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Modeling the economic benefits of an AIDS vaccine

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Abstract

Economic models were used to describe the potential for an AIDS vaccine to prevent medical spending and lost productivity throughout the world. In terms of avoided medical spending, preventing 75% of the AIDS risk for 10 years in one adult male is estimated to be worth US$ 343 in western Europe, US$ 4.59 in south and SE Asia, and US$ 2.67 in sub-Saharan Africa. The expected medical savings from a 75% effective vaccine would exceed US$ 25.00 per person for over 700 million people. Although an AIDS vaccine would save more lives in poverty stricken areas, it would save more money in developed countries. The mismatch between the public health needs and market forces is highlighted by this model. © 2001 Published by Elsevier Science Ltd.

Keywords: AIDS; HIV; Vaccine; Economics; Demand; Epidemiology; Costs

1. Introduction

This paper attempts to answer the question, "What would be the expected medical savings and labor productivity savings if an AIDS vaccine were administered to the various regional populations of the world?" The answer to this question will help individuals in both the private and public sectors to prepare for the efficient and equitable development and distribution of an AIDS vaccine to slow the epidemic. Creating more effective policies requires advance preparation built on an understanding of the future market for AIDS vaccines.

This paper projects the results of simple cost–benefit criteria as applied to the latest data on the epidemiology and economics of this disease. It would be unusual and undesirable if cost–benefit considerations exactly determined whom in the world eventually received AIDS vaccine. Nevertheless, limited budgets make economic considerations an unavoidable part of setting priorities in disease control. The exercises presented here attempt to model future cost–benefit studies of AIDS vaccines by applying cost–benefit analysis to a hypothetical AIDS vaccine of 75% effectiveness with a 10-year duration. We recognize that unforeseen changes in the fundamental determinants of demand for an AIDS vaccine will occur between now and the time when a vaccine is released, but the current model permits a timely preview of many economic issues surrounding HIV vaccine. Although there is no vaccine available yet, there is already high interest in establishing today a policy framework to speed access to an AIDS vaccine once one is discovered [1–3]. This model is intended to inform policy-makers about what future cost–benefit analyses of AIDS vaccine may show.

2. Methods

2.1. Health sector versus societal perspective

Economic benefits of AIDS vaccine are modeled as prevented expenditures related to disability and death from AIDS. Two alternative models depict the standard perspectives on the costs of an illness: (1) *the health sector perspective* in which the cost of an illness equals the net present value of the sum of all medical care costs incurred; and (2) *the societal perspective* in which the lost economic productivity is included as well as medical costs [4]. The

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full societal impact of AIDS also includes intangible costs of AIDS in terms of suffering and social upheaval that are potentially quite large but difficult to measure. A country's decision to purchase the AIDS vaccine could be motivated by either of these two perspectives on the cost of disease. The strategy that currently appears to be most prevalent for vaccine purchase decisions by health ministries is the health sector perspective in which the government health ministry is allocated a fixed budget and asked to allocate purchases for all items (often including vaccines) to maximize a population's health under that budget.

2.2. AIDS vaccine characteristics

Assumptions about the characteristics of AIDS vaccine are based on known properties of current vaccines for other diseases. AIDS vaccines under consideration could have three potential effects on the disease: (1) reduce pre-exposure susceptibility to infection; (2) slow disease progression to AIDS; and (3) reduce virus shedding. Our model will consider only the first effect because it is both simplest to model and because personal susceptibility is the foremost concern in a purchase decision by an uninfected person and/or a clinician deciding on their behalf.

In the baseline model, efficacy is assumed such that 75% of recipients who receive a complete course develop 100% protective immunity whether immunized pre- or post-exposure. Vaccine developers and their funders have no expectation that the initial vaccine trials will achieve sterilizing immunity in all recipients. There is widespread concern that a vaccine that protects only half of its recipients may not be licensed for fear that it could lead to offsetting risk behavior. A baseline efficacy of 75% was chosen to represent a vaccine that was of intermediate protection.

It is assumed that the vaccine's protection will last at least 10 years. If the initial generation of AIDS vaccine turns out to have lower efficacy and duration, the model could be adapted accordingly. The models do not take into account the possibility that a vaccine may lower the degree of shedding of infectious particles or offer therapeutic benefit.

Our model profiles potential vaccine consumers by first dividing the world's population into major geographical regions. Within each region, the general population is disaggregated by gender and by age group (0–14, 15–64, >65).

2.3. Modeling vaccine benefits

The following model of benefits predicts that financial benefits from AIDS vaccines depend on local economic factors:

$$\text{benefit of } V_j \text{ to the health sector} = \text{PV}[E \times I_{jt} \times (1 + N_{jt}) \times \text{HC}_{jt}] \quad (1)$$

where PV denotes present value computed at a 3% discount rate for a 10-year duration; V_j a decision to vaccinate everybody in group "j" where j is defined by age, gender, and world region; E vaccine efficacy from 0 to 100%, assumed = 75% for exactly 10 years in baseline analysis; I_{jt} incidence of AIDS or likelihood that average person in group j will develop AIDS in year t; N_{jt} the number of active secondary cases caused by group j and detected in year t; HC_{jt} health care costs in year t for group j. All health care costs are attributed to the same year in which a case develops.

Eq. (1) corresponds to the "health sector perspective" — it reflects a health minister's efforts to minimize the government's financial burden from HIV.

Economic benefits are computed from a societal perspective that includes lost productivity as follows:

$$\text{benefit of } V_j \text{ to society} = \text{PV}[E \times I_{jt} \times (1 + N_{jt}) \times (\text{HC}_{jt} + W_{jt})] \quad (2)$$

where W_{jt} are lost wages in year t for group j due to death and disability from AIDS.

Eq. (2) corresponds to the "societal perspective"— it reflects the considerations of a minister of finance searching for investments to both curtail medical costs and improve economic productivity.

To indicate the degree of inequity in vaccine distribution inherent in these two simple algorithms, both models were recalculated to estimate benefits throughout the world based on each group's AIDS incidence, but with monetary values for medical spending and lost productivity *from western Europe*. This corresponds to an "*equity perspective*" in that regional variation in the benefit from AIDS vaccine reflects only variation in incidence and rates of disease transmission-not the vagaries of local medical spending and GDP.

Collapsing the complex dynamics of an AIDS epidemic into a single equation offers tremendous simplicity and enables transparent comparisons of vaccine benefits across geographic regions.

The models were run using secondary data for each regional subgroup on HIV incidence [5,6], medical care costs [7], and GDP/capita [8]. People whose estimated benefits exceeded a given price were considered to be potential buyers at that price. Cumulative numbers of buyers were tallied whose modeled benefits exceeded a range of possible AIDS vaccine prices from US$ 1.00 to 100.00. Population estimates used the latest demographic data for cohorts defined by age and sex [9]. The equations underlying the model required data on health care costs, productivity costs, and vaccine administration costs for each subgroup. Table 1 summarizes estimates of costs incurred per AIDS case used in the baseline models. Table 1 shows both the present discounted value of a single HIV seroconversion in terms of medical spending, and present discounted value of lost productivity. Details on how each of these estimates was assembled is presented in a separate publication [10].

Table 1
Lifetime value lost per new case of AIDS by age and region[a]

Region	Infants/toddlers (age 0–4) (US$)	School children (age 5–14) (US$)	Average for adults (age 15–49) (US$)
Western Europe, medical (societal[b])	255014 (573552)	255014 (683102)	255014 (583263)
North Africa and middle east, medical (societal)	1335 (103300)	1335 (138368)	1335 (117525)
Sub-Saharan Africa, medical (societal)	38 (16140)	38 (21678)	38 (18386)
South and SE Asia, medical (societal)	441 (53829)	441 (72190)	441 (61277)
Eastern Europe and central Asia, medical (societal)	5035 (31274)	5035 (40298)	5035 (34934)
China, medical (societal)	1896 (10972)	1896 (14093)	1896 (12238)
Japan, medical (societal)	150591 (801166)	150591 (1024909)	150591 (821001)
South Korea, medical (societal)	67031 (218860)	67031 (271077)	67031 (223489)
East Asia and Pacific, medical (societal)	2820 (25151)	2820 (32831)	2820 (28266)
Australia and New Zealand, medical (societal)	122163 (409977)	122163 (508961)	122163 (418752)
North America, medical (societal)	299894 (650616)	299894 (771235)	299894 (661309)
Caribbean, medical (societal)	3322 (68946)	3322 (91515)	3322 (78101)
Latin America, medical (societal)	1942 (42683)	1942 (56694)	1942 (48366)

[a] Numbers in cell are the lifetime value of medical savings from preventing a single case of HIV seroconversion. Numbers in parentheses add to the medical costs the lifetime value of productivity savings. All estimates are given in year 2000 US dollars and discounted at 3%. Parameters underlying these estimates are discussed elsewhere [10].
[b] Societal refers to the sum of medical and productivity losses.

3. Results

Given the estimates of AIDS risk, vaccine efficacy, and the economic loss, the benefit from 10 years of 75% risk elimination is computed for each target group using Eq. (1) for the health sector perspective, and Eq. (2) for the societal perspective; see Tables 2 and 3. For example, sub-Saharan Africa results (Table 2) indicate that in terms of prevented medical spending, eliminating 75% of the AIDS risk for 10 years for an African man would be worth US$ 2.67. In addition, benefits from both prevented medical spending and lost productivity (Table 3) show that eliminating 75% of the AIDS risk for 10 years for an African man would be worth US$ 1531. Model results embodying market related values of worth confirm the common perception that financial markets would value AIDS prevention more highly in established market economies.

The parenthesized values in Tables 2 and 3 were derived by substituting western European costs for the costs from the various regions to reflect the premise that all lives should be valued equally. This counts all AIDS consequences throughout the world on the same dollar value scale. These parenthesized values show that Africa, Asia, and the Caribbean are regions with the greatest opportunity to prevent AIDS consequences. This demonstrates the disparity between public health priorities and financial rewards: areas with the greatest opportunity to save lives are areas where there is the least financial reward to do so.

Table 2
Health sector perspective estimates[a]

	Infants/toddlers (age 0–4) (US$)	Children/teens (age 5–14) (US$)	Women (age 15–49) (US$)	Men (age 15–49) (US$)
More developed countries				
Western Europe	31.61 (31.61)	105.39 (105.39)	87.13 (87.13)	342.87 (342.87)
Australia and New Zealand	−2.10 (0.19)	16.02 (38.02)	0.51 (5.64)	72.00 (154.87)
North America	87.94 (74.15)	262.94 (222.96)	209.51 (177.52)	850.66 (722.73)
Japan	−1.10 (0.69)	17.62 (32.41)	0.83 (3.97)	77.66 (133.07)
South Korea	−3.88 (−3.77)	16.12 (173.40)	1.19 (15.54)	31.05 (129.13)
Less developed countries				
North Africa and middle east	−0.41 (17.04)	−0.06 (82.63)	−0.15 (66.01)	0.89 (265.53)
Sub-Saharan Africa	−0.10 (2656.19)	1.07 (10513.90)	2.61 (20818.01)	2.67 (21238.58)
South and SE Asia	−0.30 (112.70)	1.23 (999.10)	1.32 (1051.71)	4.59 (2945.69)
East Europe and central Asia	−0.22 (13.66)	9.74 (518.01)	8.14 (437.36)	31.80 (1635.70)
East Asia and Pacific (excluding China, Japan, South Korea)	−0.34 (13.66)	1.40 (170.90)	0.46 (86.02)	6.12 (598.58)
China	−0.47 (4.19)	0.90 (188.12)	0.17 (90.04)	4.44 (663.44)
Caribbean	5.12 (430.80)	27.91 (2180.90)	36.63 (2849.86)	76.03 (5874.73)
Latin America	0.05 (71.09)	4.05 (597.18)	2.86 (440.87)	14.35 (1948.86)

[a] Net expected benefit of vaccination by group and by region. Numbers in parentheses are the values that would be obtained if the ability to pay in that region were equal to that of western Europe. Negative values indicate that the savings to the medical sector from vaccination do not exceed vaccine delivery costs.

Table 3
Societal perspective estimates[a]

	Infants/toddlers (age 0–4) (US$)	Children/teens (age 5–14) (US$)	Women (age 15–49) (US$)	Men (age 15–49) (US$)
More developed countries				
Western Europe	76.34 (76.34)	289.38 (289.38)	204.69 (204.69)	789.62 (789.62)
Australia and New Zealand	2.87 (5.69)	80.08 (108.92)	11.97 (18.33)	257.01 (359.63)
North America	195.71 (172.03)	682.81 (604.30)	467.07 (411.45)	1880.91 (1658.43)
Japan	11.41 (6.82)	143.16 (93.87)	22.35 (14.51)	441.18 (311.06)
South Korea	−3.62 (−3.21)	0.00 (473.22)	13.31 (40.97)	112.85 (300.76)
Less developed countries				
North Africa and middle east	6.61 (38.95)	44.61 (222.19)	30.15 (151.61)	122.10 (607.96)
Sub-Saharan Africa	167.64 (5974.66)	893.29 (28164.31)	1500.50 (47615.30)	1530.82 (48577.24)
South and SE Asia	23.40 (254.11)	282.47 (2677.11)	252.33 (2406.10)	707.43 (6737.97)
East Europe and central Asia	1.24 (31.34)	81.44 (1388.44)	59.48 (1000.96)	223.64 (3741.80)
East Asia and Pacific (excluding China, Japan, South Korea)	0.90 (31.34)	21.57 (458.63)	9.09 (197.38)	65.90 (1369.71)
China	−0.30 (10.04)	9.92 (504.75)	3.84 (206.57)	31.36 (1518.05)
Caribbean	116.11 (969.54)	782.33 (5842.79)	872.46 (6518.80)	1798.86 (13437.25)
Latin America	11.48 (160.52)	132.38 (1600.51)	83.21 (1008.99)	369.22 (4458.06)

[a] Net expected benefit of vaccination by group and by region. Numbers in parentheses are the values that would be obtained if the financial consequences of HIV/AIDS in that region were equal to that of western Europe. Negative values indicate that the savings to the GDP from vaccination do not exceed vaccine delivery costs.

3.1. Cumulative numbers of vaccine users at different prices

Figs. 1 and 2 tally the cumulative number of people whose benefits exceed a range of possible prices for AIDS vaccine. Fig. 1 does this according to the health sector decision rule. Fig. 2 shows the curve that would be generated from the societal perspective.

For example, in Fig. 1, from a health sector perspective, one sees that close to 1 billion people today would reckon the benefits of a 75% effective, 10-year duration AIDS vaccine to exceed US$ 10.00 based on the expected value of AIDS medical spending. At any vaccine price, a greater number of people reckon AIDS vaccine cost beneficial under the societal perspective as shown in Fig. 2.

3.2. Sensitivity tests

To test the robustness of the model to the estimates of vaccine effectiveness, the curves in Figs. 1 and 2 were re-estimated with the assumption that vaccine effectiveness was as high as 90% and as low as 50% retaining all other assumptions unchanged. The model did not incorporate the conjecture that vaccines with low rates of effectiveness could lead individuals to increase their risk behavior. These alternative curves are displayed as dotted lines in the figures. The sensitivity tests indicate that the less effective vaccine would attract similar numbers of potential buyers at prices that are generally half the size of a 75% effective vaccine. The model's sensitivity to vaccine effectiveness becomes more pronounced at higher prices. Other tests of sensitivity

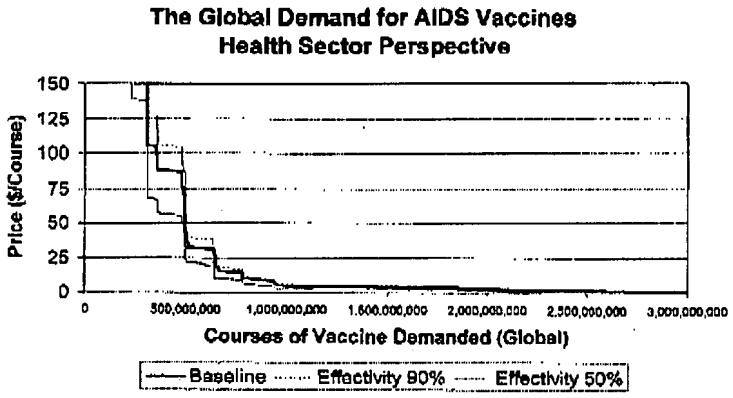

Fig. 1. Number of potential vaccine buyers as a function of the price of a complete course of vaccine. Solid line defines potential buyers using the health sector model (Eq. (1)) and assumes full course of vaccine lowers each recipient's AIDS risk by 75% for exactly 10 years. Dotted lines assume different rates of vaccine effectiveness.

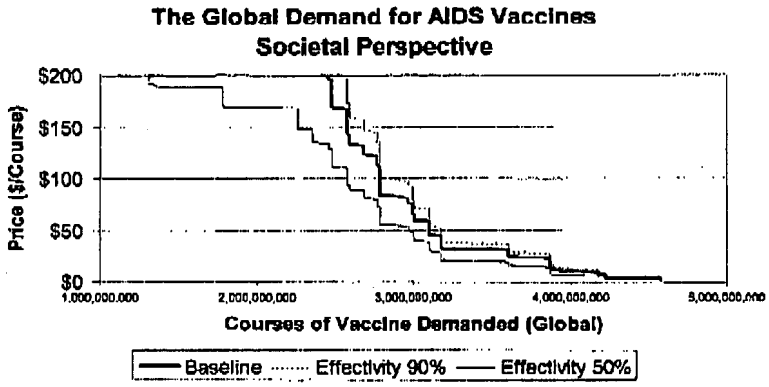

Fig. 2. Number of potential vaccine buyers as a function of the price of a complete course of vaccine. Solid line defines potential buyers using the societal model (Eq. (2)) and assumes full course of vaccine lowers each recipient's AIDS risk by 75% for exactly 10 years. Dotted lines assume different rates of vaccine effectiveness.

to the cost assumptions and incidence assumptions generate similar plots to those in Figs. 1 and 2, and are available elsewhere [10].

4. Discussion

One limitation of the model is the quality of the data on which it is based. Estimates of HIV seroincidence for many important subpopulations are not precisely known. Aggregating incidence rates across large geographic regions can obscure the dissimilarities between many individual countries and their regional geographic neighbors. Regional aggregates were used for all countries except east Asia where seroincidence and economic consequences of HIV/AIDS were so dissimilar between Japan, China, and South Korea that these three countries had to be analyzed separately from the rest of east Asia.

Another limitation is the application of population derived disease risk measures to individuals. Risk is a population measure and for a disease like HIV/AIDS many people are able to take steps to control that risk through individual behavioral change. The population incidence rates observed in the late 1990s were generated as the end result of millions of individuals, each behaving with more or less risk according to their knowledge, ability, and concern at the time. Over time the cost–benefit analysis of AIDS vaccine will change as individuals and cultures adapt to safer lifestyles. If a vaccine turns out to be very costly, many individuals would be expected to continue to use simple behavioral measures rather than costly vaccines to control their risk.

The cost consequences of HIV/AIDS are likely to increase over time, making the current measures of benefit conservative. The primary reason for increasing costs is the expected increase in the world population of current HIV/AIDS patients who will begin to receive effective HIV/AIDS therapies. Combination HIV therapies may not necessarily increase the cost of 1 year of treatment for established AIDS patients in developed countries [11].

The essential result of Table 1 is that the economic benefits of prevented medical spending per patient vaccinated are highest in developed countries and lowest in less developed countries. *This is opposite to where the greatest epidemiological benefit would be.* Although the financial benefits from AIDS vaccines are lower in developing countries, our models suggest that it is premature to write off regions like Latin America, the Caribbean, south and SE Asia as regions where the market cannot assist in the distribution of vaccines. Our model shows that health ministries in many less developed regions of the world are likely to find it cost–beneficial to actively purchase AIDS vaccines for selected populations at non-negligible prices. The societal perspective (Table 3 and Fig. 2) can be interpreted to indicate that given the opportunity to make their own purchase, a significantly large proportion of the developing world would find it cost–beneficial to buy an AIDS vaccine.

Although investments in technology can often make products better and cheaper later in the product lifecycle, one must contemplate the genuine possibility of several years spent with an AIDS vaccine whose production costs are high — perhaps higher than US$ 10.00 per course. Health ministries in regions like Africa would be reluctant to purchase such a vaccine because US$ 10.00 per person would exhaust the average annual health ministry budget. The benefit models predict that at a price of US$ 10.00 per course of vaccine, health ministries would require roughly US$ 8.00–9.00 for purchase subsidies per person to make it both affordable and optimal to purchase vaccine and invest in its distribution. The societal model predicts that in contrast to health ministries, treasury departments in every region of the world ought to be willing to spend US$ 10.00 per citizen on AIDS vaccination for large portions of the teenage and adult populations. Such investment decisions would pay their way through enhanced survival of working populations. Indeed,

there is a growing recognition that confronting AIDS is not just a health issue, but a development issue [12].

5. Conclusion

This paper has displayed the results from two models of AIDS vaccine benefit based on the prevailing inequity in the distribution of wealth and medical care. The financial value of the vaccine is highest among populations with abundant wealth, but relatively low HIV incidence. The results point to an alternative model of allocation based on equitably achieving improvements in global public health. The equity model we considered was based on what the response would be if populations with higher the HIV/AIDS risk had the financial resources of western Europeans.

The results demonstrate that financing the distribution of AIDS vaccine solely within the fixed budget of a ministry of health could exclude large and vulnerable populations from vaccine receipt. This offers a strong reminder that HIV/AIDS must be considered a developmental and security issue affecting an entire economy. Nevertheless, allocation of AIDS vaccine based on the impact of AIDS on the entire local economy would still exclude large numbers of poor infants who would be immunized if they were born in more developed regions. Furthermore, the genuine possibility of production costs for vaccine higher than US$ 10.00 per course would require a vaccine purchase fund of much larger size than planned if the goal were to create global equity in access to the AIDS vaccine.

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Appendix 4

(4)

Vaccinating First-Year College Students Living in Dormitories for Meningococcal Disease

An Economic Analysis

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Background: Surveillance of meningococcal disease among U.S. college students found an elevated rate of this disease among first-year students living in dormitories.

Objective: This study examines the economics of routinely vaccinating a cohort of 591,587 incoming first-year students who will live in dormitories for ≥1 years.

Methods: A cost–benefit model (societal perspective) was constructed to measure the net present value (NPV) of various vaccination scenarios, as well as the cost/case and cost/death averted. Input values included hospitalization costs from $10,924 to $24,030 per hospitalization; immunization costs (vaccine plus administration costs) from $54 to $88 per vaccine; 30 nonfatal, vaccine-preventable cases over a 4-year period (includes 3 with sequelae); 3 premature deaths; value of human life from $1.2 million to $4.8 million; and long-run sequelae costs from $1298 to $14,600. Sensitivity analyses were also conducted on vaccine efficacy (80% to 90%); discount rate (0% to 5%); and coverage (60% to 100%).

Results: The costs of vaccination outweighed the benefits gained with NPVs ranging from −$11 million to −$49 million. The net cost per case averted ranged from $0.6 million to $1.9 million. The net cost per death averted ranged from $7 million to $20 million. The break-even costs of vaccination (when NPV=$0) at 60% coverage ranged from $23 (90% vaccine efficacy) to $5 (80% efficacy).

Conclusions: The model showed that the vaccination program is not cost-saving. Key variables influencing the results were the low number of vaccine-preventable cases and the high cost of vaccination. However, from the perspective of students and parents, the cost of vaccination might be worth the real or perceived benefit of reducing the risk to an individual student of developing meningococcal disease.

Medical Subject Headings (MeSH): economics, cost–benefit analysis, adolescence, universities, meningococcal infections, meningococcal vaccines (Am J Prev Med 2002;23(2): 98–105)

Introduction

Neisseria meningitidis is the leading cause of bacterial septicemia and meningitis in children and young adults in the United States, with high case fatality and morbidity despite good medical care. Disease rates are highest among infants and are increasing among adolescents and young adults.[1] Of 32 reported outbreaks of meningococcal disease between July 1994 and July 1997, four occurred on college campuses.[2] Two thirds of cases are from meningococcal serogroups C, Y, or W135, for which an effective vaccine for older children and adults is available. In 1995, Jackson et al.[3] evaluated the costs and benefits of a vaccination program for U.S. college students.[3] The authors used rates of disease of people aged 18 to 23 years because rates among college students were unavailable. The estimated cost of this program was $45 million annually. Given the low incidence of disease, the authors felt that a program targeted at higher-risk subgroups of college students might be cost effective.

New data sources allow for refinement of that model to evaluate high-risk groups. In 1998, a new surveillance system was initiated to track the incidence of meningococcal disease among U.S. college students. Data from

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Table 1. Valuations of benefits[a] and costs[b] of vaccination: five scenarios

Variable	Scenarios				
	Low	Intermediate	High	Worst	Best
Benefits[a]					
Hospital days per case[c]	7 days (2 ICU)	11 days (3 ICU)	15 days (4 ICU)	7 days (2 ICU)	15 days (4 ICU)
Costs per hospitalization[d]	$10,924	$16,998	$24,030	$10,924	$24,030
Value of life lost[e] and associated discount rate	$1,205,127 (5% SDR[e])	$1,205,127 (5% SDR)	$4,800,000	$1,205,127 (5% SDR)	$4,800,000
	$1,818,762 (3% SDR)	$1,818,762 (3% SDR)		$1,818,762 (3% SDR)	
	$2,940,582 (1% SDR)	$2,940,582 (1% SDR)		$2,940,582 (1% SDR)	
Cost of treating a case of sequelae[f]	$1298	$5708	$14,530	$1298	$14,530
Costs[b]					
Cost of vaccine[g]	$36	$52	$68	$68	$36
Vaccine administration[h]	$18	$18	$20	$20	$18
Treatment of side effects[i]	$3500 per 500,000 doses	$3500 per 500,000 doses	$2454 per case; 1 case per 100,000	$2454 per case; 1 case per 100,000	$3500 per 500,000 doses

[a]Benefits are the savings associated with cases and deaths averted.
[b]Costs are those associated with vaccination.
[c]The low estimate is based on Jackson et al.[5] The high estimate is based on information from the Allegheny County, Pennsylvania, Health Department (J. Fellows, Centers for Disease Control and Prevention, unpublished observations data, 1999). The intermediate estimate is the midpoint between the high and the low estimate.
[d]These estimates are for the costs of acute care only. The estimate used for the low and intermediate scenarios is from Jackson et al.,[5] adjusted for inflation to July 1999 prices using the health services component of the Consumer Price Index. The high estimate costs come from the Allegheny County, Pennsylvania Health Department (LJE and PDW, unpublished observations, 1999).
[e]For the low, intermediate, and worst scenarios, a life lost was valued using different age-weighted productivity estimates for the group aged 16 to 19 years under the three different discount rates. All the productivity estimates were derived based on a 1% productivity growth rate,[25] amended and updated to 1998 (Fellows, unpublished observations, 1999). For the high and best scenarios, a life lost was valued at the value of a statistical life.[18–20]
[f]The cost estimates for first/year, acute sequelae treatment costs, and the value of lifetime productivity losses were developed using information from Erickson and De Wals (unpublished observations, 1999). The benefit–cost model, developed by Jackson et al.,[5] did not consider treatment costs for long-term sequelae due to lack of evidence. Evidence from Quebec province shows that 1.5% of victims suffering some type of sequelae had multiple amputations of legs and arms, while another 3% had loss of a single limb or loss of toes or fingers.[11] Another 12% of victims had skin scarring. While it is reasonable to assume that cases of multiple amputations experience either a loss in economic well-being or some loss in lifetime productivity, this analysis uses the following range of estimates due to lack of concrete data: 30% as high, 10% as intermediate, and 0% as low. The productivity/loss figure used to calculate these estimates is $2.94 million (0% discount, 1% productivity growth). Cost information from Allegheny County, Pennsylvania ($15,500 medical cost for amputations and $5,000 for treatment of skin scarring) (LJE and PDW, unpublished observations, 1999) was used to calculate a high, an intermediate, and low long-term sequelae cost estimate as a weighted average, with the weights being the probability of the above outcomes occurring. The calculations follow:

High:

$$[(\$2,940,582 \times 0.30 \times 0.015) + (\$15,500 \times 0.015)] + (\$15,500 \times 0.03) + (\$5,000 \times 0.12) = \$14,530$$

Intermediate:

$$[(\$2,940,582 \times 0.10 \times 0.015) + (\$15,500 \times 0.015)] + (\$15,500 \times 0.03) + (\$5,000 \times 0.12) = \$5,708$$

Low:

$$[(\$2,940,582 \times 0.0 \times 0.015) + (\$15,500 \times 0.015)] + (\$15,500 \times 0.03) + (\$5,000 \times 0.12) = \$1,298$$

There is insufficient information to develop an appropriate estimate of the long-term direct and indirect lifetime medical costs due to disease-related amputations. For the above calculations, these costs are not included.
[g]The estimate used for the low and best scenarios is the wholesale price for a 10-dose vial at $36 per dose.[21] The estimate used for the high and worst scenarios is the wholesale price for a single dose vial at $68 per dose.[21] The estimate used for the intermediate scenario is an average ($52) of the low and high estimates per dose.
[h]The estimate used for the low, intermediate, and worst scenarios is from Jackson et al.[5] adjusted for inflation to July 1999 prices using the health services component of the Consumer Price Index. The estimate used for the high and worst scenarios comes from LJE and PDW (unpublished observations, 1999).
[i]For the low, intermediate, and best scenarios, the number of side effects is based on incidence rates from Yergeau et al.,[26] with one case of anaphylaxis per million doses (2 days hospitalization) and one severe reaction (one medical consultation) per 10,000 doses. Total treatment costs = $7000 per million doses (LJE and PDW, unpublished observations, 1999). The estimate used for the high and worst scenarios is from Jackson et al.,[5] which is based on one severe systemic reaction per 100,000 doses. These treatment costs were adjusted for inflation to July 1999 prices using the health services component of the Consumer Price Index.
ICU, intensive care unit; SDR, social discount rate.